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(54) Title: CONTROLLED-RELEASE DOSAGE FORMS OF AZITHROMYCIN

(57) Abstract

A controlled-release dosage form of azithromycin having an improved side effect profile; a process for preparing the dosage form; and a method of treating a microbial infection, comprising administering azithromycin in such a controlled-release dosage form to a mammal, including a human patient, in need of such treatment.

Controlled-Release Dosage Forms of Azithromycin

FIELD OF THE INVENTION

This invention relates to a controlled-release dosage form of azithromycin having an improved side effect profile, to a process for preparing the dosage form, and to a method of treating a microbial infection, comprising administering azithromycin in such a controlled-release dosage form to a mammal, including a human patient, in need of such treatment.

BACKGROUND OF THE INVENTION

Azithromycin is the U.S.A.N. (generic name) for 9a-aza-9a-methyl-9-deoxo-9a-homoerythromycin A, a broad spectrum antimicrobial compound derived from erythromycin A. Azithromycin was independently discovered by Bright, U.S. Pat. No. 4,474,768 and Kobrehel et al., U.S. Pat. No. 4,517,359. These patents disclose that azithromycin and certain derivatives thereof possess antimicrobial properties and are accordingly useful as antibiotics.

It is widely known that oral dosing of azithromycin can result in the occurrence, in some patients, of adverse gastrointestinal (GI) side effects, such as cramping, diarrhea, nausea, and vomiting. In combined clinical studies of azithromycin involving 3,995 patients (all dose levels combined), 9.6% of patients reported gastrointestinal side effects. The most frequent of these side effects were diarrhea (3.6%), nausea (2.6%), and abdominal pain (2.5%) (Hopkins, Am. J. Med. 91(suppl 3A) (1991) 40S-45S).

The incidence of gastrointestinal side effects is higher at higher doses than at lower doses. For example, a common 5 day course of azithromycin therapy consists of 500 mg on day 1 followed by 250 mg on days 2, 3, 4, and 5. For this course of therapy, the reported incidence of various gastrointestinal side effects was 5% diarrhea/loose stools, 3% abdominal pain, and 3% nausea (Zithromax (Trademark of Pfizer Inc.) capsule package insert). After a single 1 g oral dose, the reported incidence of various gastrointestinal side effects was 7% diarrhea/loose stools, 5% nausea, and 2% vomiting (Zithromax capsule package insert).

It is also known that azithromycin can cause gastrointestinal side-effects in non-human mammals, e.g. dogs.

not more than about 40 mg of azithromycin per kg of mammal weight in the first 6 hours after ingestion.

The above criteria are herein referred to as the "weight criteria".

In a further specific aspect, the invention provides an oral delayed release dosage form of azithromycin, comprising azithromycin and a pharmaceutically acceptable carrier, which releases not more than about 10% of its incorporated azithromycin in the stomach, and which releases no more than an additional 10% during the first 15 minutes after the dosage form has entered the duodenum. Once having entered the duodenum and moved distally through and beyond this intestinal segment for at least 15 minutes, the rate at which the dosage form releases azithromycin is not critical, so long as substantially all of the azithromycin therein is released for absorption, as opposed to being excreted.

In a further specific aspect, this invention provides a sustained release dosage form, comprising azithromycin and a pharmaceutically acceptable carrier, which releases a total amount of azithromycin at the following rate following ingestion by a mammal: not more than about 200 mg azithromycin total in the first 15 minutes after ingestion, not more than about 500 mg of azithromycin total in the first hour after ingestion, not more than about 1000 mg total in the first two hours after ingestion, not more than about 1500 mg total in the first four hours after ingestion, and not more than about 2000 mg total in the first six hours after ingestion. The preceeding criteria are referred to herein as the "temporal criteria". Rates of azithromycin release lower than the rate just described are also within the scope of the invention and may produce even better side effect profiles, particularly for patients under 50kg weight, e.g., children. Thus an azithromycin release rate of (each amount representing the total (i.e., cumulative) amount released), for example, less than 200 mg in the first 15 minutes after ingestion, less than 400 mg in the first hour after ingestion, less than 750 mg in the first two hours after ingestion, less than 1250 mg in the first 4 hours after ingestion, and less than 1500 mg in the first 6 hours after ingestion represents a release profile within the scope of the invention and may be even more efficacious for ameliorating side effects. Once six hours following ingestion has passed, the rate at which the dosage form releases azithromycin (for example, if the dosage form contained more than 2 g of azithromycin to begin with) is not critical. The rate must, of course, be high

In the case of sustained release embodiments, the dosage form can be in the form of a tablet, a capsule, a multiparticulate form, or a unit dose packet (sometimes referred to in the art as a "sachet").

The term "tablet" is intended to embrace compressed tablets, coated tablets, matrix tablets, osmotic tablets, and other forms known in the art, as more fully disclosed below.

The term "capsule" is intended to embrace capsules in which the body of the capsule disintegrates after ingestion to release particulate contents which exhibit the desired sustained-release behavior, and also capsules for which the body of the capsule remains substantially intact during its residence in the GI tract.

The term "multiparticulate" is intended to embrace a dosage form comprising a multiplicity of particles whose totality represents the intended therapeutically useful dose of azithromycin. The particles generally are of a diameter from about 50 microns to about 0.3 cm, with a preferred range of 100 μM to 1 mm. The use of these and other terms is more fully set out below. Multiparticulates represent a preferred embodiment for sustained-release because they are amenable to use in scaling dosage forms according to the weight of an individual animal (e.g., a horse), according to the weight criteria previously set forth, by simply scaling the number of particles in the dosage form to conform with the animal's weight.

In a further aspect, this invention provides a process for preparing sustained-release dosage forms of azithromycin, comprising the steps of granulating azithromycin bulk drug substance with a binder, essentially immediately thereafter coating the granulation with a polymer coating of controlled permeability to azithromycin, and thereafter further coating said granulation with additional polymer of controlled permeability to azithromycin until enough of the polymer has been applied to effect the desired sustained release rate or profile.

In a further aspect, this invention provides a method for treating a microbial infection, comprising administering to a mammal in need of such treatment, including a human patient, a therapeutically effective amount of azithromycin in a controlled-release oral dosage form which releases the azithromycin according to the release rate described above.

In the case of delayed release embodiments, the dosage form can be in the form of a tablet, capsule, multiparticulate, suspension, or sachet,

exposure of azithromycin throughout the GI tract, specially at the duodenum, thereby providing decreased gastrointestinal side effects.

It is noted that controlled-release dosage forms of various types are known and employed conventionally in the art to provide reduced dosing frequency for short half-life compounds and to reduce fluctuations in plasma concentrations, sometimes imparting an improved safety/efficacy profile. Because elimination of azithromycin from the human body is characterized by a long half-life of about 69 hours, however, it is surprising that a controlled-release (either sustained or delayed) dosage form would offer any benefit.

BRIEF DESCRIPTION OF THE DRAWINGS

FIGURE 1 is a graphical illustration of a release profile as broadly defined by the temporal criteria (profile 1), of several hypothetical azithromycin release profiles within the scope of the invention (profiles 3 and 4), and of a hypothetical release profile outside the scope of the invention (profile 2).

DETAILED DISCUSSION

For the purpose of this application, various embodiments of "controlled release dosage forms of azithromycin" have been described as "sustained release" embodiments or "delayed release" embodiments, for ease of description. Without intending to be limiting, sustained release dosage forms of azithromycin are those which slowly release azithromycin. Delayed release dosage forms of azithromycin are those which release little or no azithromycin for a predetermined time, then release azithromycin quickly or in a sustained fashion. It will be appreciated by those skilled in the art that certain "sustained release" embodiments will also fall under the general rubric of "delayed release" embodiments, and vice versa. For example, sustained release osmotic pump devices generally exhibit a "lag time" after ingestion, during which time the osmotic pressure in the device is increasing and during which time little or no drug is released. Thus, an azithromycin osmotic pump device may be considered both a sustained release and a delayed release device. Embodiments of the current invention include all controlled release dosage forms of azithromycin which meet one or both of the in vitro tests described herein (see "Examples"

radius (cm)		diffusion coefficient (cm^2/s)
0.0025	(50µm diameter)	1.7×10^{-10}
0.1	(2mm diameter)	3×10^{-7}
0.5	(1cm diameter)	7×10^{-6}

The above table illustrates that diffusion coefficients change by orders of magnitude as the desired size of the device changes. The high and low values represent approximate upper and lower limits for matrix devices of this invention. That is, materials which exhibit a diffusion coefficient lower than about 10^{-10} are likely unsuitable for this invention as they are approaching, relatively speaking, being totally impermeable to azithromycin. Materials characterized by a diffusion coefficient higher than about 7×10^{-6} are likely also unsuitable as they are approaching, relatively speaking, being an instant or fast-release device. Materials at the low end of the diffusion coefficient scale are polymers such as cellulose acetate. Conversely, materials at the upper end of the scale are materials such as hydrogels. The rate of diffusion for any particular device can accordingly be tailored by the material or materials selected.

In the same manner but different words, in general, sustained release devices of this invention should be implemented to release the azithromycin contained therein over a period of up to 6 h, and possibly longer. The device can accordingly be engineered according to the equation $RT = r^2/D$ wherein RT stands for the total release time of a contained dosage, r represents the radius of the device, and D stands for the diffusion coefficient of azithromycin in the matrix material. The equation again illustrates that suitable dosage forms can be engineered as a trade-off between the size of the device and the diffusion coefficient of the matrix material. If a spherical dosage form is not employed, then r will, of course, be replaced by other suitable dimension as known in the art, such as the half thickness of a cube, short axis for an ellipsoid, and the like.

For purposes of further illustration, to obtain a sustained-release matrix in a particle of about 50µm in diameter, a matrix material of a polymer such as cellulose acetate or a similar material will likely be required, the slow diffusing matrix material tending to offset the tendency of the small particle size to diffuse quickly. By contrast, in order to obtain sustained-

release-modifying agents include water-soluble materials such as sugars or salts. Preferred water-soluble materials include lactose, sucrose, glucose, and mannitol, as well as HPC, HPMC, and PVP.

A preferred process for manufacturing matrix multiparticulates is the extrusion/spheronization process. For this process, the azithromycin is wet-massed with a binder, extruded through a perforated plate or die, and placed on a rotating disk. The extrudate ideally breaks into pieces which are rounded into spheres, spheroids, or rounded rods on the rotating plate. A preferred process and composition for this method involves using water to wet-mass a blend comprising about 20 to 75% of micro-crystalline cellulose blended with, correspondingly, about 80 to 25% azithromycin.

A further preferred process for manufacturing matrix multiparticulates is the preparation of wax granules. In this process, a desired amount of azithromycin is stirred with liquid wax to form a homogeneous mixture, cooled and then forced through a screen to form granules. Preferred matrix materials are waxy substances. Especially preferred are hydrogenated castor oil and carnauba wax and stearyl alcohol.

A further preferred process for manufacturing matrix multiparticulates involves using an organic solvent to aid mixing of the azithromycin with the matrix material. This technique can be used when it is desired to utilize a matrix material with an unsuitably high melting point that, if the material were employed in a molten state, would cause decomposition of the drug or of the matrix material, or would result in an unacceptable melt viscosity, thereby preventing mixing of azithromycin with the matrix material. Azithromycin and matrix material may be combined with a modest amount of solvent to form a paste, and then forced through a screen to form granules from which the solvent is then removed. Alternatively, azithromycin and matrix material may be combined with enough solvent to completely dissolve the matrix material and the resulting solution (which may contain solid drug particles) spray dried to form the particulate dosage form. This technique is preferred when the matrix material is a high molecular weight synthetic polymer such as a cellulose ether or cellulose ester. Solvents typically employed for the process include acetone, ethanol, isopropanol, ethyl acetate, and mixtures of two or more.

Once formed, azithromycin matrix multiparticulates may be blended with compressible excipients such as lactose, microcrystalline cellulose,

dosage form can be used to advantage to make the release rate of the drug more constant as detailed below.

In a further embodiment, an azithromycin matrix tablet is coated with an impermeable coating, and an orifice (for example, a circular hole or a rectangular opening) is provided by which the content of th tablet is exposed to the aqueous GI tract. These embodiments are along the lines of those presented in in U.S. 4,792,448 to Ranade, herein incorporated by reference. The opening is typically of a size such that the area of the exposed underlying azithromycin composition constitutes less than about 40% of the surface area of the device, preferably less than about 15%.

In a preferred embodiment, an azithromycin matrix tablet is coated with an impermeable material on part of its surface, e.g. on one or both tablet faces, or on the tablet radial surface.

In a preferred embodiment, an azithromycin matrix tablet is coated with an impermeable material and an opening for drug transport produced by drilling a hole through the coating. The hole may be through the coating only, or may extend as a passageway into the tablet.

In a further preferred embodiment, an azithromycin matrix tablet is coated with an impermeable material and a passageway for drug transport produced by drilling a passageway through the entire tablet.

In a further preferred embodiment, an azithromycin matrix tablet is coated with an impermeable material and one or more passageways for drug transport are produced by removing one or more strips from the impermeable coating or by cutting one or more slits through the coating, preferably on the radial surface or land of the tablet.

In a preferred embodiment, an azithromycin matrix tablet is shaped in the form of a cone and completely coated with an impermeable material. A passageway for drug transport is produced by cutting off the tip of the cone.

In a further preferred embodiment, an azithromycin matrix tablet is shaped in the form of a hemisphere and completely coated with an impermeable material. A passageway for drug transport is produced by drilling a hole in the center of the flat face of the hemisphere.

In a further preferred embodiment, an azithromycin matrix tablet is shaped in the form of a half-cylinder and completely coated with an impermeable material. A passageway for drug transport is produced by cutting a slit through (or removing a strip from) the impermeable coating

for highly water-swollen gels, the diffusion coefficient of the drug in the gel may approach the value in pure water. This high diffusion coefficient permits practical release rates from relatively large devices (i.e., it is not necessary to form microparticles). Although hydrogel devices can be prepared, loaded with azithromycin, stored, dispensed and dosed in the fully hydrated state, it is preferred that they be stored, dispensed, and dosed in a dry state. In addition to stability and convenience, dry state dosing of hydrogel devices provides good azithromycin release kinetics. Preferred materials for forming hydrogels include hydrophilic vinyl and acrylic polymers, polysaccharides such as calcium alginate, and poly(ethylene oxide). Especially preferred are poly(2-hydroxyethyl methacrylate), poly(acrylic acid), poly(methacrylic acid), poly(N-vinyl-2-pyrolidinone), poly(vinyl alcohol) and their copolymers with each other and with hydrophobic monomers such as methyl methacrylate, vinyl acetate, and the like. Also preferred are hydrophilic polyurethanes containing large poly(ethylene oxide) blocks. Other preferred materials include hydrogels comprising interpenetrating networks of polymers, which may be formed by addition or by condensation polymerization, the components of which may comprise hydrophilic and hydrophobic monomers such as those just enumerated.

A second class of azithromycin sustained-release dosage forms of this invention includes membrane-moderated or reservoir systems. In this class, a reservoir of azithromycin is surrounded by a rate-limiting membrane. The azithromycin traverses the membrane by mass transport mechanisms well known in the art, including but not limited to dissolution in the membrane followed by diffusion across the membrane or diffusion through liquid-filled pores within the membrane. These individual reservoir system dosage forms may be large, as in the case of a tablet containing a single large reservoir, or multiparticulate, as in the case of a capsule containing a plurality of reservoir particles, each individually coated with a membrane. The coating can be non-porous, yet permeable to azithromycin (for example azithromycin may diffuse directly through the membrane), or it may be porous. As with other embodiments of this invention, the particular mechanism of transport is not believed to be critical.

Sustained release coatings as known in the art may be employed to fabricate the membrane, especially polymer coatings, such as a cellulose ester or ether, an acrylic polymer, or a mixture of polymers. Preferred

capsule may be prepared independently of the drug composition, thus process conditions that would adversely affect the drug can be used to prepare the capsule. A preferred embodiment is a capsule having a shell made of a porous or a permeable polymer made by a thermal forming process. An especially preferred embodiment is a capsule shell in the form of an asymmetric membrane; i.e., a membrane that has a thin skin on one surface and most of whose thickness is constituted of a highly permeable porous material. A preferred process for preparation of asymmetric membrane capsules comprises a solvent exchange phase inversion, wherein a solution of polymer, coated on a capsule-shaped mold, is induced to phase-separate by exchanging the solvent with a miscible non-solvent. Examples of asymmetric membranes useful in this invention are disclosed in the aforementioned European Patent Specification 0 357 369 B1.

A preferred embodiment of the class of reservoir systems comprises a multiparticulate wherein each particle is coated with a polymer designed to yield sustained release of azithromycin. The multiparticulate particles each comprise azithromycin and one or more excipients as needed for fabrication and performance. The size of individual particles, as previously mentioned, is generally between about 50 μm and about 3 mm, although beads of a size outside this range may also be useful. In general, the beads comprise azithromycin and one or more binders. As it is generally desirable to produce dosage forms which are small and easy to swallow, beads which contain a high fraction of azithromycin relative to excipients are preferred. Binders useful in fabrication of these beads include microcrystalline cellulose (e.g., Avicel®, FMC Corp.), hydroxypropyl cellulose (HPC), hydroxypropyl methyl cellulose (HPMC), and related materials or combinations thereof. In general, binders which are useful in granulation and tabletting, such as starch, pregelatinized starch, and poly (N-vinyl-2-pyrrolidinone) (PVP) may also be used to form multiparticulates.

Reservoir system azithromycin multiparticulates may be prepared using techniques known to those skilled in the art, including, but not limited to, the techniques of extrusion and spheronization, wet granulation, fluid bed granulation, and rotary bed granulation. In addition, the beads may also be prepared by building the azithromycin composition (drug plus excipients) up on a seed core (such as a non-pareil seed) by a drug-layering technique such as powder coating or by applying the azithromycin composition by

coating dries, a phase inversion takes place in the applied coating solution, resulting in a membrane with a porous structure.

A preferred embodiment is a multiparticulate comprising about 95% azithromycin, the individual particles being coated with an aqueous dispersion of ethyl cellulose, which dries to form a continuous film.

A further preferred embodiment is obtained when the azithromycin beads are less than about 400 µm in size and are coated with a phase inversion membrane of ethyl cellulose or cellulose acetate.

An especially preferred embodiment is obtained when the azithromycin beads are less than about 400 µm in size and are coated with an aqueous dispersion of ethyl cellulose, which dries to form a continuous film.

An even more especially preferred embodiment is obtained when the azithromycin beads are less than about 300 µm in size and are coated with an aqueous dispersion of ethyl cellulose, which dries to form a continuous film.

A third class of azithromycin sustained-release dosage forms includes the osmotic delivery devices or "osmotic pumps" as they are known in the art. Osmotic pumps comprise a core containing an osmotically effective composition surrounded by a semipermeable membrane. The term "semipermeable" in this context means that water can pass through the membrane, but solutes dissolved in water cannot. In use, when placed in an aqueous environment, the device imbibes water due to the osmotic activity of the core composition. Owing to the semipermeable nature of the surrounding membrane, the contents of the device (including the drug and any excipients) cannot pass through the non-porous regions of the membrane and are driven by osmotic pressure to leave the device through an opening or passageway pre-manufactured into the dosage form or, alternatively, formed *in situ* in the GI tract as by the bursting of intentionally-incorporated weak points in the coating under the influence of osmotic pressure. The osmotically effective composition includes water-soluble species, which generate a colloidal osmotic pressure, and water-swellable polymers. The drug itself (if highly water-soluble) may be an osmotically effective component of the mixture. Azithromycin fumarate has a solubility at pH 7 of about 100mg/ml, corresponding to an osmotic pressure of about 3 atmospheres, enough to contribute some osmotic driving force. However,

When placed in an aqueous medium, the tablet imbibes water through the membrane, causing the azithromycin composition to form a dispensible aqueous composition, and causing the hydrogel layer to expand and push against the azithromycin composition, forcing the azithromycin composition out of the exit passageway.

The rate of azithromycin delivery is controlled by such factors as the permeability and thickness of the coating, the water activity of the hydrogel layer, and the surface area of the device. Those skilled in the art will appreciate that increasing the thickness of the coating will reduce the release rate, whereas increasing the permeability of the coating or the water activity of the hydrogel layer or the surface area of the device will increase the release rate.

Exemplary materials which are useful to form the azithromycin composition, in addition to the azithromycin itself, include hydroxypropyl methyl cellulose, poly (ethylene oxide), poly (N-vinyl-2-pyrrolidinone) or PVP, and other pharmaceutically-acceptable carriers. In addition, osmagents such as sugars or salts, especially sucrose, mannitol, or sodium chloride, may be added. Materials which are useful for forming the hydrogel layer include sodium carboxymethyl cellulose, poly (ethylene oxide), poly (acrylic acid), sodium (poly-acrylate) and other high molecular-weight hydrophilic materials. Particularly useful are poly (ethylene oxide) having a molecular weight from about 4,000,000 to about 7,500,000 and sodium carboxymethyl cellulose having a molecular weight of about 200,000 to about 1,000,000.

Materials which are useful for forming the coating are cellulose esters, cellulose ethers, and cellulose ester-ethers. Preferred are cellulose acetate and ethylcellulose.

The exit passageway must be located on the side of the tablet containing the azithromycin composition. There may be more than one such exit passageway. The exit passageway may be produced by mechanical or by laser drilling, or by creating a difficult-to-coat region on the tablet by use of special tooling during tablet compression. The rate of azithromycin delivery from the device may be optimized so as to provide a method of delivering azithromycin to a mammal for optimum therapeutic effect.

discussed for reservoir systems. Suitable and preferred polymer coating materials, equipment, and coating methods also include those previously discussed.

Materials useful for preparing the second coating on the tablet include polymers known in the art as enteric coatings for delayed-release of pharmaceuticals. Th se most commonly are pH-sensitive materials such as cellulose acetate phthalate, cellulose acetate trimellitate, hydroxypropyl methyl cellulose phthalate, poly (vinyl acetate phthalate), and acrylic copolymers such as Eudragit L-100 (Röhm Pharma) and related materials, as more fully detailed below under "Delayed Release". The thickness of the delayed-release coating is adjusted to give the desired delay property. In general, thicker coatings are more resistant to erosion and, consequently, yield a longer delay. Preferred coatings range from about 300µm in thickness to about 3mm in thickness.

When ingested, the twice-coated tablet passes through the stomach, where the second coating prevents release of the azithromycin under the acidic conditions prevalent there. When the tablet passes out of the stomach and into the small intestine, where the pH is higher, the second coating erodes or dissolves according to the physicochemical properties of the chosen material. Upon erosion or dissolution of the second coating, the first coating prevents immediate or rapid release of the azithromycin and modulates the release so as to prevent the production of high concentrations, thereby minimizing side-effects.

A further preferred embodiment comprises a multiparticulate wherein each particle is dual coated as described above for tablets, first with a polymer designed to yield sustained release of the azithromycin and then coated with a polymer designed to delay onset of release in the environment of the GI tract when the dosage form is ingested. The beads contain azithromycin and may contain one or more excipients as needed for fabrication and performance. Multiparticulates which contain a high fraction of azithromycin relative to binder are preferred. The multiparticulate may be of a composition and be fabricated by any of the techniques previously disclosed for multiparticulates used to make reservoir systems (including extrusion and spheronization, wet granulation, fluid bed granulation, and rotary bed granulation, seed building, and so forth).

carriers, such core being coated with a material, preferably a polymer, which is substantially insoluble and impermeable at the pH of the stomach, and which is more soluble and permeable at the pH of the small intestine. Preferably, the coating polymer is substantially insoluble and impermeable at pH <5.0, and water-soluble at pH>5.0. It is also preferred that the tablet core be coated with an amount of polymer sufficient to assure that substantially no release of azithromycin from the dosage form occurs until the dosage form has exited the stomach and has resided in the small intestine for about 15 minutes or greater, preferably about 30 minutes or greater, thus assuring that minimal azithromycin is released in the duodenum. Mixtures of a pH-sensitive polymer with a water-insoluble polymer may also be employed. Tablets are coated with an amount of polymer comprising from about 10% to about 80% of the weight of the azithromycin-containing tablet core. Preferred tablets are coated with an amount of polymer comprising about 15% to about 50% of the weight of the azithromycin tablet core.

pH-sensitive polymers which are relatively insoluble and impermeable at the pH of the stomach, but which are more soluble and permeable at the pH of the small intestine and colon include polyacrylamides, phthalate derivatives such as acid phthalates of carbohydrates, amylose acetate phthalate, cellulose acetate phthalate, other cellulose ester phthalates, cellulose ether phthalates, hydroxypropylcellulose phthalate, hydroxypropylethylcellulose phthalate, hydroxypropylmethylcellulose phthalate, methylcellulose phthalate, polyvinyl acetate phthalate, polyvinyl acetate hydrogen phthalate, sodium cellulose acetate phthalate, starch acid phthalate, styrene-maleic acid dibutyl phthalate copolymer, styrene-maleic acid polyvinylacetate phthalate copolymer, styrene and maleic acid copolymers, polyacrylic acid derivatives such as acrylic acid and acrylic ester copolymers, polymethacrylic acid and esters thereof, poly acrylic methacrylic acid copolymers, shellac, and vinyl acetate and crotonic acid copolymers.

Preferred pH-sensitive polymers include shellac; phthalate derivatives, particularly cellulose acetate phthalate, polyvinylacetate phthalate, and hydroxypropylmethylcellulose phthalate; polyacrylic acid derivatives, particularly polymethyl methacrylate blended with acrylic acid

approximately 6.0 and th pH of the colon is approximately 7.0, coatings composed of mixtures of Eudragit-L® and Eudragit-S® provide protection of the duodenum from azithromycin. If it is desired to delay release of azithromycin until the azithromycin-containing "pH-dependent coated tablet" has reached the colon, Eudragit-S® may be used as the coating material, as described by Dew et al (Br. J. Clin. Pharmac. 14 (1982) 405-408). In order to delay the release of azithromycin for about 15 minutes or more, preferably 30 minutes or more, after the dosage form has exited the stomach, preferred coatings comprise from about 9:1 to about 1:9 Eudragit-L®/Eudragit-S®, more preferably from about 9:1 to about 1:4 Eudragit-L®/Eudragit-S®. The coating may comprise from about 3% to about 70% of the weight of the uncoated tablet core. Preferably, the coating comprises from about 5% to about 50% of the weight of the tablet core.

In a further embodiment, a "pH-dependent coated bead", beads (about 0.5 to 3.0 mm in diameter) comprising azithromycin plus carrier are coated with one or more of the aforementioned pH-sensive polymers. The coated beads may be placed in a capsule or may be compressed into a tablet, with care taken to avoid damaging the polymeric coat on individual beads during tablet compression. Preferred coated beads are those which exhibit substantially no release of azithromycin from the dosage form until the beads have exited the stomach and have resided in the small intestine for about 15 minutes or greater, preferably about 30 minutes or greater, thus assuring that minimal azithromycin is released in the duodenum. Mixtures of a pH-sensitive polymer with a water-insoluble polymer are also included. As described above, azithromycin-containing beads may be coated with mixtures of polymers whose solubilities vary at different pH's. For example, preferred coatings comprise from about 9:1 to about 1:9 Eudragit-L®/Eudragit-S®, more preferably from 9:1 to 1:4 Eudragit-L®/Eudragit-S®. The coating may comprise from about 5% to about 200% of the weight of the uncoated bead core. Preferably, the coating comprises from about 10% to about 100% of the weight of the bead core.

In a further embodiment, ("pH-dependent coated particle"), small azithromycin-containing particles (about 0.01 to 0.5 mm in diameter, preferably 0.05 to 0.5 mm in diameter) are coated with one or more of the aforementioned pH-sensitive polymers. The coated particles may be placed in a capsule or may be compressed into a tablet, with care taken to avoid

In a further embodiment ("bursting osmotic core device"), azithromycin is incorporated in an osmotic bursting device which comprises a tablet core or bead core containing azithromycin and, optionally, one or more osmagents. Devices of this type have been generally disclosed in Baker, US 3,952,741, which is incorporated herein by reference. Examples of osmagents are sugars such as glucose, sucrose, mannitol, lactose, and the like; and salts such as sodium chloride, potassium chloride, sodium carbonate, and the like; water-soluble acids such as tartaric acid, fumaric acid, and the like. The azithromycin-containing tablet core or bead core is coated with a polymer which forms a semipermeable membrane, that is, a membrane which is permeable to water but is substantially impermeable to azithromycin. Examples of polymers which provide a semipermeable membrane are cellulose acetate, cellulose acetate butyrate, and ethylcellulose, preferably cellulose acetate. The semipermeable coating membrane may alternatively be composed of one or more waxes, such as insect and animal waxes such as beeswax, and vegetable waxes such as carnauba wax and hydrogenated vegetable oils. A melt mixture of a polyethylene glycol, e.g., polyethylene glycol-6000, and a hydrogenated oil, e.g., hydrogenated castor oil, may be used as a coating, as described for isoniazid tablets by Yoshino (Capsugel Symposia Series; Current Status on Targeted Drug Delivery to the Gastrointestinal Tract; 1993; pp.185-190). Preferred semipermeable coating materials are cellulose esters and cellulose ethers, polyacrylic acid derivatives such as polyacrylates and polyacrylate esters, and polyvinyl alcohols and polyalkenes such as ethylene vinyl alcohol copolymer. Especially preferred semipermeable coating materials are cellulose acetate and cellulose acetate butyrate.

When a coated tablet or bead of the "bursting osmotic core" embodiment of this invention is placed in an aqueous environment of use, water passes through the semipermeable membrane into the core, dissolving a portion of the azithromycin and osmagent, generating a colloidal osmotic pressure which results in bursting of the semipermeable membrane and release of azithromycin into the aqueous environment. By choice of bead or tablet core size and geometry, identity and quantity of osmagent, and thickness of the semipermeable membrane, the time lag between placement of the dosage form into the aqueous environment of use and release of the enclosed azithromycin may be chosen. It will be appreciated by those

azithromycin until about 15 min or more, preferably 30 minutes or more, after the dosage form has exited the stomach. A bursting osmotic core device which releases azithromycin about 1.5 hr after ingestion will decrease the incidence and severity of gastrointestinal side effects in a population of patients administered azithromycin in such devices. A preferred bursting osmotic core device starts to release azithromycin at about 2.5 hr after entering an aqueous environment, i.e., after ingestion, to more reliably assure that the device releases its azithromycin distal to the duodenum, when dosed in the fasted state. A more preferred "bursting osmotic core device" will start to release azithromycin at about 4 hr after entering an aqueous environment. This 4 hr delay permits dosing in the fed state, and allows for an about 3.5 hr retention in the fed stomach, followed by an approximately 30 minute delay after the dosage form has exited from the stomach. In this way, the release of azithromycin into the most sensitive portion of the gastrointestinal tract, the duodenum, is minimized.

In a further embodiment, a "bursting coated swelling core", an azithromycin-containing tablet or bead is prepared which also comprises 25-70% of a swellable material, such as a swellable colloid (e.g., gelatin), as described in Milosovich, US 3,247,066, incorporated herein by reference. Preferred swelling core materials are hydrogels, i.e., hydrophilic polymers which take up water and swell, such as polyethylene oxides, polyacrylic acid derivatives such as polymethyl methacrylate, polyacrylamides, polyvinyl alcohol, poly-N-vinyl-2-pyrrolidone, carboxymethylcellulose, starches, and the like. Preferred swelling hydrogels for this embodiment are polyethylene oxides and carboxymethylcellulose. The colloid/hydrogel-containing azithromycin-containing core tablet or bead is coated, at least in part, by a semipermeable membrane. Examples of polymers which provide a semipermeable membrane are cellulose acetate and cellulose acetate butyrate,and ethylcellulose, preferably cellulose acetate. The semipermeable coating membrane may alternatively be composed of one or more waxes, such as insect and animal waxes such as beeswax, and vegetable waxes such as carnauba wax and hydrogenated vegetable oils. A melt mixture of a polyethylene glycol, e.g., polyethylene glycol-6000, and a hydrogenated oil, e.g., hydrogenated castor oil, may be used as a coating, as described for isoniazid tablets by Yoshino (Capsugel Symposia Series; Current Status on Targeted Drug Delivery to the Gastrointestinal Tract;

the same consideration and preferences apply to making bursting coated swelling core devices.

In a further embodiment, a "pH-triggered osmotic bursting device", azithromycin is incorporated into a device of the type described in allowed commonly assigned co-pending US patent 5,358,502, issued October 25, 1994, incorporated herein by reference. The device comprises azithromycin and optionally one or more osmagents, surrounded at least in part by a semipermeable membrane. The semipermeable membrane is permeable to water and substantially impermeable to azithromycin and osmagent. Useful osmagents are the same as those described above for bursting osmotic core devices. Useful semipermeable membrane materials are the same as those described above for bursting osmotic core devices. A pH-trigger means is attached to the semipermeable membrane. The pH-trigger means is activated by a pH above 5.0, and triggers the sudden delivery of the azithromycin. In this embodiment, the pH-trigger means comprises a membrane or polymer coating which surrounds the semipermeable coating. The pH-trigger coating contains a polymer which is substantially impermeable and insoluble in the pH range of the stomach, but becomes permeable and soluble at about the pH of the duodenum, about pH 6.0.

Exemplary pH-sensitive polymers are polyacrylamides, phthalate derivatives such as acid phthalates of carbohydrates, amylose acetate phthalate, cellulose acetate phthalate, other cellulose ester phthalates, cellulose ether phthalates, hydroxypropylcellulose phthalate, hydroxypropylethylcellulose phthalate, hydroxypropylmethylcellulose phthalate, methylcellulose phthalate, polyvinyl acetate phthalate, polyvinyl acetate hydrogen phthalate, sodium cellulose acetate phthalate, starch acid phthalate, styrene-maleic acid dibutyl phthalate copolymer, styrene-maleic acid polyvinylacetate phthalate copolymer, styrene and maleic acid copolymers, polyacrylic acid derivatives such as acrylic acid and acrylic ester copolymers, polymethacrylic acid and esters thereof, poly acrylic methacrylic acid copolymers, shellac, and vinyl acetate and crotonic acid copolymers.

Preferred pH-sensitive polymers include shellac; phthalate derivatives, particularly cellulose acetate phthalate, polyvinylacetate phthalate, and hydroxypropylmethylcellulose phthalate; polyacrylic acid derivatives, particularly polymethyl methacrylate blended with acrylic acid

coated with a 3-20% by weight membrane composed of about 1:1 cellulose acetate/cellulose acetate phthalate. Another preferred pH-triggered osmotic bursting device is a bead or tablet core of azithromycin with optional osmagent, coated with a 3-20% by weight cellulose acetate membrane, coated with a 3-20% by weight membrane comprising from about 9:1 to about 1:1 Eudragit-L®/Eudragit-S®.

Advantageously, because a pH-triggered osmotic bursting device possesses a mechanism for sensing that the device has exited the stomach, interpatient variability in gastric emptying is not significant.

In a further embodiment, a "pH-triggered bursting coated swelling core", a tablet core or bead containing azithromycin and a swelling material is coated with a semipermeable coating which is further coated with a pH-sensitive coating. The core composition, including choice of swelling material is as described above for the bursting coated swelling core embodiment. The choice of semipermeable coating material and pH-sensitive coating material are as described above for the "pH-triggered osmotic core" embodiment. This device is described in detail in commonly-assigned copending U.S. Patent Application Serial No. 08/023,227, filed February 25, 1993, incorporated herein by reference.

A pH-triggered bursting swelling core embodiment generally operates as follows. After oral ingestion, the pH-trigger coating, which surrounds the semi-permeable coating, which in turn surrounds the azithromycin-containing core tablet or bead, remains undissolved and intact in the stomach. In the stomach, water may or may not commence penetration through the pH-trigger coating and the semipermeable coating, thus starting hydration of the core, which contains azithromycin and water-swellable material, preferably a hydrogel. When the pH-triggered bursting swelling core device exits the stomach and enters the small intestine, the pH-trigger coating rapidly disintegrates and dissolves, and water passes through the semipermeable coating, dissolving azithromycin and swelling the water-swellable material within the core. As the swelling pressure across the semipermeable coating exceeds some threshold value, the semipermeable coating fails, and the device bursts, releasing azithromycin. It is preferred that this bursting and release of azithromycin occur at about 15 minutes or more, preferably about 30 minutes, after the pH-triggered

gastrointestinal system is delayed until about 15 minutes or more, preferably about 30 minutes, after the dosage form has exited the stomach and moved into the duodenum.

In an azithromycin enzyme-triggered supported liquid membrane device, the supported hydrophobic liquid is preferably a liquid which undergoes change which is enzymatically catalyzed in the lumen of the small intestine, and not in the stomach. Exemplary hydrophobic liquids are triglycerides, fatty anhydrides, fatty acid esters of cholesterol, hydrophobic amino acid esters, and the like. Preferred triglycerides include triolein, tricaprylin, trilaurin, olive oil, palm oil, coconut oil, sesame seed oil, corn oil, peanut oil, soybean oil, and the like. Preferred fatty acid anhydrides include caprylic anhydride, lauric anhydride, myristic anhydride and the like. Mixtures of hydrophobic liquids may be used. Exemplary materials for the microporous hydrophobic support membrane include cellulose esters, polycarbonates, polyalkenes, polystyrenes, polyvinyl esters, polysiloxanes, polyacrylates, and polyethers. Preferably the hydrophobic microporous membrane with entrained hydrophobic liquid is impermeable to azithromycin, until gastrointestinal enzymes have catalyzed a change in the hydrophobic oil, as described below.

In the environment of use, i.e., the small intestinal lumen, lipases and esterases degrade the aforementioned hydrophobic oils, releasing surfactant products in the pores of the microporous membrane of this embodiment, thus producing aqueous channels through which the azithromycin in the device core may exit through the microporous hydrophobic support membrane. Release of the azithromycin may occur by simple diffusion, osmotic pumping, osmotic bursting, or by bursting due to the presence of a swellable material, e.g., hydrogel, in the azithromycin-containing core of the device.

In an azithromycin enzyme-triggered supported liquid membrane device, hydrophobic oils may be used which are substrates for small intestinal proteases such as carboxypeptidase and chymotrypsin. Exemplary oils are hydrophobic esters of amino acid derivatives.

In a further embodiment, a "bacterially degradable coating device", azithromycin-containing tablets or beads are coated with a material which is substantially impermeable to azithromycin in the stomach and small intestine, the coating material undergoing degradation by bacteria or by

materials, including but not limited to polyethylene, polypropylene, poly(methylmethacrylate), polyvinylchloride, polystyrene, polyurethanes, polytetrafluoroethylene, nylons, polyformaldehydes, polyesters, cellulose acetate, and nitrocellulose. The open end of the capsule shell is then "plugged" with a cylindrical plug formed from a hydrogel-forming material, including but not limited to, a homo- or co-poly(alkylen oxide) crosslinked by reaction with isocyanate or unsaturated cyclic ether groups, as described in PCT Application WO 90/09168. The composition and length of the hydrogel "plug" is selected to minimize release of azithromycin to the stomach and duodenum, to decrease the incidence and/or severity of gastrointestinal side effects. The plugged capsule-half is finally sealed with a water-soluble, e.g., gelatin, capsule-half placed over the hydrogel-plugged end of the azithromycin-containing non-dissolving capsule-half. In a preferred embodiment of the "swelling plug device", the sealed device is coated with a "pH-sensitive enteric polymer or polymer mixture", for example cellulose acetate phthalate or copolymers of methacrylic acid and methylmethacrylate. The weight of the enteric polymer coat will generally be from 2-20%, preferably from 4-15% of the weight of the uncoated sealed capsule. When this preferred "enteric-coated swelling plug device" is ingested orally, the enteric coat prevents release of azithromycin in the stomach. The enteric coat dissolves quickly, e.g., within about 15 minutes, in the duodenum, triggering swelling of the hydrogel plug, exiting of the hydrogel plug, and release of the incorporated azithromycin into the gastrointestinal tract at a time greater than about 15 minutes after, and preferably greater than about 30 minutes after, the dosage form has passed from the stomach into the duodenum. Prototype unfilled "swelling plug devices" may be obtained from Scherer DDS Limited, Clydebank, Scotland, under the designation "Pulsincap™".

It will be appreciated by those skilled in the art that the various coated azithromycin tablet, bead, and particle embodiments described above can be coated using standard coating equipment, such as pan coaters (e.g., Hi-Coater available from Freund Corp; Accela-Cota available from Manesty, Liverpool), fluidized bed coaters, e.g., Wurster coaters, (available from Glatt Corp, Ramsey, NJ and Aeromatic Corp., Columbia, MD), and rotary granulators, e.g., CF-Granulator (available from Freund Corp). Core tablets

subscript. Thus, a "$Q_{0.25}$" of 15 mg means that 15 mg of azithromycin was dissolved in one quarter hour.

2. Specification of a quantity in percent (%) means percent by weight based on total weight, unless otherwise indicated.

3. "Eudragit® " is the registered trademark of Röhm Pharma GmbH, Germany for a family of enteric polymeric methacrylates.

4. "Opadry® " is the registered trademark of Colorcon Inc., West Point, PA for a family of plasticized cellulose ethers which include hydroxypropyl methylcellulose, hydroxypropyl cellulose and methylcellulose that are supplied as powders for reconstitution in water.

5. "Surelease® " is the registered trademark of Colorcon Inc., West Point, PA for an aqueous, fully plasticized polymeric dispersion of ethylcellulose.

6. "mgA" is an abbreviation for "milligrams of active azithromycin". For example, "250 mg A" means 250 mg of active azithromycin".

7. "X mgA of multiparticulate" (where X is a number) means the amount of multiparticulate containing X mgA. For example, "250 mgA of multiparticulate" means the weight of multiparticulate containing 250 mgA.

8. "mgAm" is an abbreviation for "mgA of multiparticulate".

9. "Use environment" means the aqueous environment of the gastrointestinal tract.

10. ***In Vitro Dissolution Tests*** The following two *in vitro* tests can be used to screen sustained release and delayed release embodiments of this invention for *in vivo* suitability. If a particular dosage form satisfies the criteria disclosed below for either test, it is within the scope of the invention.

Sustained Release Dosage Test: Sustained release dosage forms of azithromycin are tested in a standard USP rotating paddle apparatus as disclosed in United States Pharmacopoeia XXIII (USP) Dissolution Test Chapter 711, Apparatus 2. Paddles are rotated at 50 rpm and the dissolution test is conducted in, as the test medium, 900 mL of pH 6.0 sodium dihydrogen phosphate buffer at 37°C. If capsules are used, then 0.1 mg/mL of the enzyme trypsin must be added to the buffer. At indicated times following test initiation (i.e., insertion of the dosage form into the apparatus), filtered aliquots (typically 5 or 10 mL) from the test medium are analyzed for azithromycin by high performance liquid chromatography (HPLC) as disclosed below. Dissolution results are reported as mg

containing the same stationary phase. The chromatography system is substantially as described in Shepard et al., J. Chromatography, 565: 321-337 (1991). An isocratic mobile phase consisting of 72 % 0.02M potassium phosphate monobasic buffer and 28 % acetonitrile (v/v, final pH of 11) is employed at a flow rate of 1.5 mL/min. The electrochemical detector employs dual glassy carbon electrodes (Model LC-4B amperometric detector, Bioanalytical Systems, West Lafayette, IN) operating in the oxidative screen mode with the reference electrode set at about +0.7 V and the working electrode set at about +0.8 V. In sustained-release test media, actual quantification of azithromycin is effected by comparison of sample chromatogram peak height ratio relative to diphenhydramine internal standard against an azithromycin standard chromatogram peak height ratio also relative to the same internal standard. In delayed-release (acid) test media, because azithromycin can hydrolyze in acid media to desosaminylazithromycin, the amount of dissolved azithromycin which had hydrolyzed is determined and converted to its equivalent as azithromycin (conversion factor, 1.26). In delayed-release test media, diphenhydramine is again employed as an internal peak height reference standard for both sample and azithromycin/desosaminylazithromycin standard chromatograms.

12. Where no value is given in the Tables, it was not determined.

Example 1

This example demonstrates that a 2 g oral dose of azithromycin gives a similar incidence of gastrointestinal side effects, whether the 2 g is given as a single oral dose or as eight 250 mg doses, given as 250 mg every half-hour for 3.5 hr.

In a double-blind, randomized, placebo-controlled parallel group study, healthy male subjects were divided into three groups. Group A received a single 2 g azithromycin dose as eight 250 mg azithromycin capsules ("bolus dosing" group). Group B received the same total dose, administered as eight 250 mg capsules at the rate of one 250 mg capsule each 30 minutes for 3.5 hr ("divided dosing" group). Group C received matching placebo capsules. All subjects received eight capsules of drug or placebo at time 0, and a capsule of drug or placebo every half-hour for 3.5 hr. All subjects were dosed after an overnight fast. Blood samples were

subjects in the group, to give a Mean Cumulative Score. The scale of this Mean Cumulative Score does not correspond to the original 0-10 scale, since it reflects the summation of all non-zero scores over the entire evaluation period. Table III presents Mean Cumulative Scores for abdominal pain, nausea, regurgitation, and abdominal cramping.

Table I demonstrates that the total systemic azithromycin exposure of the two dosing groups, reflected in the AUC, was similar. For the divided dosing group, Cmax was lower and Tmax was longer, as expected because the dosing took place over 3.5 hr, rather than in a single bolus dose.

Table II demonstrates that abdominal pain, nausea, and abdominal cramping were frequent side effects for a 2 g bolus dose, while regurgitation was not. Divided dosing over 3.5 hr gave a similar side effect incidence profile. Table III demonstrates that the overall severity of azithromycin-induced side effects was similar for the bolus-dosing and divided dosing treatments.

The data presented in Table II and Table III demonstrate that delivering a 2 g dose at a rate of 500 mg/hr does not result in a greatly improved side effect incidence, compared with a single 2 g bolus dose. The manner in which the divided dose was administered in this example resulted in exposure of the upper gastrointestinal tract, i.e., the stomach and duodenum, to the entire divided dose.

Table I.
Azithromycin Pharmacokinetics For A
2 g Dose given as a Single Dose, or as Eight 250 mg doses every Half-Hour for 3.5 Hours (mean values).

TREATMENT	Cmax (µg/ml)	Tmax (hr)	AUC_{0-144} (µg-hr/ml)
2 g single dose	1.69	1.3	18.8
250 Mg per half-hr for 3.5 hr	1.13	4.4	18.9

the conclusion that the incidence and severity of azithromycin gastrointestinal side effects can be reduced by decreasing the exposure of the duodenum to orally dosed azithromycin. This example also demonstrates that direct delivery of azithromycin to the duodenum or the ileocecal region of the small intestine does not result in any loss of systemic bioavailability, relative to oral dosing.

Healthy male subjects were divided into two groups. Group A received a 2 g azithromycin dose administered directly into the duodenum as a solution via a nasoenteric tube. Group B received the same azithromycin solution dose, administered directly into the ileocecal region of the small intestine via a nasoenteric tube. The nasoenteric tube was a single lumen, 4.5 meter tube with a side port for delivery of drug. Placement of the tube for duodenal and ileocecal delivery was confirmed by fluoroscopy. Infusions to the duodenum or ileocecal region were administered at a concentration of 40 mg/ml within 5 minutes. All subjects were dosed after an overnight fast. Subjects were randomized to receive azithromycin and placebo via nasoenteric tube and intravenous infusion in a double-blind, placebo controlled fashion. Two weeks later, subjects were crossed over to the alternate route of active drug administration.

Blood samples were withdrawn prior to dosing, and at 0.08, 0.17, 0.33, 0.66, 1, 2, 4, 8, 12, 24, 48, 72, and 96 hr post-dosing. Serum azithromycin concentrations were determined using the high performance liquid chromatography assay described in Shepard et al., J. Chromatography, 565: 321-337 (1991). Total systemic exposure to azithromycin was determined by measuring the area under the serum azithromycin concentration vs. time curve (AUC) for each subject in a given group, and then by calculating a mean AUC for the group. Cmax is the highest serum azithromycin concentration achieved in a subject. Tmax is the time at which Cmax is achieved. Serum pharmacokinetic data for this example are presented in Table IV. In one leg of this study, all subjects received an intravenous 2 g azithromycin dose. The intravenous AUC was determined in order to calculate the absolute duodenal and ileocecal bioavailabilities, as described below.

Prior to dosing and each blood sampling time, each subject filled out a questionnaire, which consisted of a series of "Visual Analogue Scales" in which the subject was required to rate, on a scale of 0-10, the severity of

The bioavailability of the duodenal azithromycin solution was slightly larger than the oral bioavailability of an azithromycin capsule, which is typically about 38%. The bioavailability of the ileocecal azithromycin solution was similar to that of an orally dosed capsule.

Table V (same format as Table II) demonstrates that the incidence of gastrointestinal side effects is generally higher for duodenal dosing than for ileocecal dosing. Table VI demonstrates that the overall severity of gastrointestinal side effects was higher for duodenal dosing than for ileocecal dosing.

Table IV.

Azithromycin Pharmacokinetics for a 2 g Solution Dose administered to the duodenal (n=5) or ileocecal (n=6) region of the small intestine via nasoenteric tube (mean values).

TREATMENT	Cmax (µg/ml)	Tmax (hr)	AUC_{0-96} (µg•hr/ml)
Duodenal	3.24	0.3	17.0
Ileocecal	0.77	1.39	14.5

Table V.

Incidence of Visual-Analogue-Scale scores exceeding 1 or 4 at any time during the 96 hour post-dose evaluation period, for the side effects abdominal pain, nausea, regurgitation, and abdominal cramping. Compares 2 g azithromycin administration directly into the duodenal (n=5) and ileocecal (n=6) regions of the small intestine.

	ABDOMINAL PAIN		NAUSEA		REGURGITATION		ABDOMINAL CRAMPING	
TREATMENT	>1	>4	>1	>4	>1	>4	>1	>4
Duodenal	4/5	0/5	2/5	1/5	3/5	0/5	5/5	0/5
Ileo-cecal	2/6	0/6	2/6	0/6	0/6	0/6	2/6	0/6

azithromycin was determined by measuring the area under the serum azithromycin concentration vs. time curve (AUC) for each subject in a given group, and then by calculating a mean AUC for the group. Cmax is the highest serum azithromycin concentration achieved in a subject. Tmax is the time at which Cmax is achieved. Serum pharmacokinetic data for this example are presented in Table VII.

Prior to dosing and each blood sampling time, each subject filled out a questionnaire, which consisted of a series of "Visual Analogue Scales" in which the subject was required to rate, on a scale of 0-10, the severity of certain potential side effects. The subjects were instructed that "0" indicated an absent effect and "10" indicated the worst possible effect. The subjects were instructed to interpolate between 0 and 10 for moderate side effects.

A total of 22 subjects completed this study: 5 on placebo, 6 at 1 g azithromycin total dose, 6 at 2 g azithromycin total dose, and 5 at 4 g azithromycin total dose. For four side effects evaluated at 18 time points, a total of 1,584 individual visual-analogue-scale evaluations were obtained.

Analysis of side effect visual-analogue-scale data was carried out in two formats. In the first format (Table VIII), the analysis concentrated on the general incidence of side effects of a particular type. For each side effect type (e.g., abdominal pain), Table VIII reports the number of subjects who reported a score >1 at any time during the 240 hr post-dosing, and the number of subjects who reported a score >4 at any time during the 240 hr post-dosing. This analysis assumes that all scores >1 represent a real side effect occurrence, however mild or severe. A score >4 is presumed to reflect a moderate-to-severe side effect occurrence.

In the second format (Table IX), the analysis reflects the general severity and duration of side effects. For a particular side effect (e.g., Abdominal Pain) in a particular subject, all visual-analogue-scale scores (over the 240 hr post-dose period) were summed to give a "cumulative score" over the entire time period of evaluation. "Cumulative scores" for all members of a treatment group were summed, and divided by the number of subjects in the group, to give a Mean Cumulative Score. The scale of this Mean Cumulative Score does not correspond to the original 0-10 scale, since it reflects the summation of all non-zero scores over the entire evaluation period. Table IX presents Mean Cumulative Scores for abdominal pain, nausea, regurgitation, and abdominal cramping.

ileostomy fluid concentrations of azithromycin were assayed. In the 24 hr following an IV azithromycin dose, 13% of the dose was recovered intact in the ileostomy fluid, indicated that IV-administered azithromycin enters the lumen of the small intestine, probably via biliary excretion and/or transintestinal elimination. Thus it is not surprising that high intravenous doses of azithromycin can cause gastrointestinal side effects, since a portion of the IV dose partitions into the lumen of the small intestine.

Table IX demonstrates that the overall severity of gastrointestinal side effects resulting from a 1.0 g intravenous dose is low, and is lower than that observed for a 2 g oral dose (compare with Table III). Based on an oral bioavailability of 37%, these intravenous doses are equivalent to oral doses of 0, 2.7, 5.4 and 10.8 g, respectively. At higher IV doses (e.g., 4 g), gastrointestinal side effects are observed. However, it is likely that these GI side effects are due to partitioning of the IV dose into the lumen of the small intestine, as clearly demonstrated above in the ileostomy study.

Table VII.

Azithromycin Pharmacokinetics: For a 2 hr Infusion of 1 g (n=6) or 2 g (n=6) or 4 g (n=5) total dose.

TOTAL IV DOSE (g)	EQUIVALENT ORAL DOSE* (g)	C_{max} (µg/ml)	T_{max} (hr)	AUC_{0-inf} (µg-hr/ml)
1.0	2.7	3.11	1.9	23.4
2.0	5.4	6.84	1.8	45.6
4.0	10.8	9.91	1.1	82.1

* Calculated by dividing the IV dose by the oral bioavailability of azithromycin (0.37)

diffusion barrier coating. The process comprised (1) preparing uncoated azithromycin multiparticulate cores; and (2) applying a diffusion barrier coating over the cores. This example further illustrates the *in vitro* sustained release dosage test procedure for evaluating dissolution and release of azithromycin from the dosage form.

Azithromycin-containing multiparticulate cores were prepared by blending azithromycin with microcrystalline cellulose (Avicel® PH101, FMC Corp., Philadelphia, PA) in relative amounts of 95:5 (w/w), wet massing the blend in a Hobart mixer with water equivalent to approximately 27% of the weight of the blend, extruding the wet mass through a perforated plate (Luwa EXKS-1 extruder, Fuji Paudal Co.,Osaka Japan), spheronizing the extrudate (Luwa QJ-230 marumerizer, Fuji Paudal Co.) and drying the final cores which were about 1 mm diameter. The final sustained release beads were made by coating over the particle cores with a plasticized ethylcellulose dispersion (Surelease®, Colorcon, West Point, PA, typically applied at 15 % solids concentration). For example 4A (about 100 g batch size), final coating was conducted in a bottom spray Wurster fluid bed coater (Aeromatic Strea-1, Niro Inc., Bubendorf, Switzerland). For examples 4B, 4C and 4D (about 1 kg batch sizes), final coating was conducted in a rotary granulator (CF-360 granulator, Freund Indust., Tokyo, Japan). The amount of coating applied was varied to obtain different dissolution rate behavior. Example 4A had an additional coating of 2% Opadry® over the 13 % Surelease® Coat.

Finished sustained release multiparticulates were tested using the *in vitro* sustained release dosage test procedure previously described and the results are presented in Table 4-1. Example 4D was tested as 1,500 mgA multiparticulate and examples 4A through 4C were tested as 250 mgA multiparticulate in a capsule. Examples 4A through 4D satisfy the *in vitro* sustained release dissolution criteria and are sustained release embodiments within the scope of the invention.

temporal criterion. For instance the maximum scaled value at 15 minutes (12,500 mgAm) was calculated as 200 mgA x (250 mgAm ÷ 4 mgA), where the 250 mgAm corresponds to the initial dose tested. The maximum scaled value at 2 hr (2,212 mgAm) was similarly calculated as 1000 mgA x (250 mgAm ÷ 113 mgA).

Table 5-1 indicates that the maximum scaled dose of Example 4B multiparticulate which should be used to make a dosage form within the scope of the invention is 2,212 mgAm, the minimum of the maximum scaled values calculated.

Maximum scaled doses were also calculated using the temporal criteria together with the data of Examples 4A, 4C, and 4D in the same manner as above. Table 5-2 summarizes the maximum scaled dose for Examples 4A through 4D.

TABLE 5-2
MAXIMUM SCALED DOSE

Example	Maximum Scaled Dose of Sustained Release Multiparticulate
4A	2,857 mgA
4B	2,212 mgA
4C	6,024 mgA
4D	4,680 mgA

Example 6

This example illustrates using weight criteria in conjunction with *in vitro* dissolution test results to custom design a dosage form tailored for an animal of a given body weight. The data of example 4B are employed to calculate the minimum body weight for each of the weight criteria.

TABLE 6-2
Maximum Dose Deliverable To A Given Body Weight

Example	Maximum Dose Sustained Release Multiparticulate 100 kg Body Weight
4A	5,714 mgAm
4B	4,425 mgAm
4C	12,048 mgAm
4D	9,360 mgAm

Example 7

This example illustrates using the weight criteria in conjunction with *in vitro* dissolution test results to determine the minimum animal body weight with which a sustained release dosage form should be used.

A sustained release sachet containing 2000 mgAm is made with the multiparticulate of Example 4B. A minimum animal body weight was calculated for use with this sachet according to each of the weight criteria.

TABLE 7-1
Minimum Body Weights

Weight Criteria	Example 4B Dissolution Results	Minimum Scaled Body Weight for use with 2,000 mgAm
≤ 4 mg/kg in 15 min.	4 mgA in 15 min.	8 kg
≤ 10 mg/kg in 1 hr.	33 mgA in 1 hr.	26.4 kg
≤ 20 mg/kg in 2 hr.	113 mgA in 2 hr.	45.2 kg
≤ 30 mg/kg in 4 hr.	144 mgA in 4 hr.	38.4 kg
≤ 40 mgA/kg in 6 hr.	154 mgA in 6 hr.	30.8 kg

Each minimum scaled body weight was calculated by using the data of Example 4B and assuming a 2000 mgAm to calculate the smallest weight consistent with each individual corresponding weight criterion. For instance

coating suspension diluted to 15% solids was sprayed onto the rotating bed of azithromycin particles. During spray application, both agglomeration of azithromycin particles into larger particles and coating of these agglomerates with the diffusion barrier membrane occurred. In some examples, a water soluble coating of Opadry® (typically diluted to 10 % solids for spraying) was applied over the barrier membrane as added protection.

Finished sustained release multiparticulates were tested using the *in vitro* sustained release dosage test procedure previously described and the results are presented in Table 8-1. Examples 8A through 8G satisfy the *in vitro* sustained release dissolution criteria and are sustained release embodiments of the invention.

TABLE 8-1

In Vitro Sustained Release Dissolution Criteria		$Q_{0.25}$ ≤ 200	Q_1 ≤ 500	Q_2 ≤1000	Q_4 ≤ 1500	Q_6 ≤2000	
Example No. (Mean Particle Size, µm)	Surelease® Coating (%)	$Q_{0.25}$ mgA	Q_1 mgA	Q_2 mgA	Q_4 mgA	Q_6 mgA	Initial Dose Tested mgAm
8A (240 µm)	16.7	-----	110	206	216	228	228
8B (240 µm)	16.6 [1] 0.5 Opadry®	-----	191	-----	196	-----	250
8C (280 µm)	22..7 1.6 Opadry®	-----	110	141	188	214	226
8D (310 µm)	27.1	-----	104	212	257	265	272
8E (315 µm)	25.1	-----	45	74	116	138	250
8F (335 µm)	30.9	-----	-----	45	-----	119	180
8G (400 µm)	35.6 0.7 Opadry®	-----	-----	32	-----	77	166

[1] Examples 8B, 8C and 8G have a water soluble Opadry ® protective coating added over the Surelease® diffusion barrier coating. For the case of Example 8B, a 0.5 % Opadry® coating was done over a 16.6 % Surelease® coating.

As in Example 5, the data of Example 9 were employed in conjunction with the temporal criterion to calculate the maximum scaled mgAm, corresponding to both Example 9A and 9B, which should be used to make a dosage form according to the invention. Table 10-1 summarizes the maximum scaled dose for Examples 9A and 9B.

TABLE 10-1
Maximum Scaled Dose

Example	Maximum Scaled Dose of Sustained Release Multiparticulate
9 A	1,976 mgA
9 B	5,236 mgA

Example 11

This example illustrates using weight criteria in conjunction with *in vitro* test results to custom design a dosage form tailored for an animal of a given body weight.

The data from Examples 9A and 9B were employed to calculate, as in Example 6, the maximum dose which should be administered to a 100 kg animal. Table 11-1 lists the maximum amounts of sustained release multiparticulate for Examples 9A and 9B which should be employed for a given body weight of 100 kg according to the dissolution criteria and body weight criteria to make a multiparticulate dosage form within the scope of the invention.

TABLE 11-1
Maximum Dose Deliverable To A Given Body Weight

Example	Maximum Dose Sustained Release Multiparticulate 100 kg Body Weight
9 A	3,953 mgA
9 B	10,471 mgA

Table 13-1. Example 13A satisfies the *in vitro* release criteria and is a sustained release embodiment of the invention.

TABLE 13-1

In Vitro Sustained Release Dissolution Criteria		$Q_{0.25}$ ≤ 200	Q_1 ≤ 500	Q_2 ≤1,000	Q_4 ≤ 1,500	Q_6 ≤2,000	
Example	Solids Coating (%)	$Q_{0.25}$ mgA	Q_1 mgA	Q_2 mgA	Q_4 mgA	Q_6 mgA	Initial Dose Tested mgAm
13A	23.1	------	------	160	------	238	250 mgA Capsule

Example 14

This example illustrates a process for making sustained release azithromycin hydrophilic matrix tablets which release azithromycin at different rates depending on their composition. The process comprised (1) blending all components except for magnesium stearate; (2) screening and reblending the same components; (3) adding and blending magnesium stearate; and (4) compressing the final blend into tablets.

In batch sizes of 150 grams, azithromycin was shaken for about 15 minutes in a suitably large jar with all other components except magnesium stearate using a Turbula shaker system (Basel, Switzerland). Next, the blend was passed through a 40 mesh sieve and shaken again for ten minutes. Then, magnesium stearate was added and the blend was shaken for five minutes. Using a Manesty type F press (Manesty Machines, Liverpool, England) , the final blend was compressed into tablets using either 13/32 inch standard round concave (SRC) punches for Examples 14A through 14I or 3/4 inch standard round flat faced punches for Examples 14J and 14K. A summary of compositions of Examples 14A through 14K is shown in Table 14-1.

TABLE 14-2
Sustain d Release Hydrophilic Matrix Tablet Compositions

In Vitro Sustained R lease Dissolution Criteria	$Q_{0.25}$ ≤ 200	Q_1 ≤ 500	Q_2 ≤1,000	Q_4 ≤1,500	Q_6 ≤2,000	
Example	$Q_{0.25}$ (mgA)	Q_1 (mgA)	Q_2 (mgA)	Q_4 (mgA)	Q_6 (mgA)	Initial Dose Tested
8A	----	37	----	69	85	Tablet 250mgAm
8B	----	42	----	92	111	Tablet 250mgAm
8C	----	----	69	105	124	Tablet 250mgAm
8D	----	----	113	158	200	Tablet 250 mgAm
8E	----	148	175	236	249	Tablet 250 mgAm
8F	----	----	52	----	94	Tablet 250 mgAm
8G	----	----	51	----	91	Tablet 250 mgAm
8H	----	----	167	218	233	Tablet 250 mgAm
8I	----	----	109	135	150	Tablet 250 mgAm
8J	80	201	276	413	481	Tablet 1000 mgAm
8K	88	144	183	245	290	Tablet 1000 mgAm

Example 15

This example illustrates a process for making multiparticulates for use in making delayed-release dosage forms designed to release azithromycin predominantly below the duodenum. The process comprised (1) preparing uncoated azithromycin multiparticulate cores; (2) applying a first, sustained-release coating over the cores; and (3) applying a second , pH-sensitive, delayed-release coating over the first coat. This example further illustrates

TABLE 15-1

In Vitro Delayed Release Dosage Test Dissolution Criteria		$Q_{0.25}$ ≤ 10 %	$Q_{0.5}$ ≤ $Q_{0.25}$ +10 %	
Example	Formulation Composition, (%)	$Q_{0.25}$ (Acid Stage)	$Q_{0.5}$ (Buffer Stage)	Initial D s (mgAm)
15A	Immediate-Release Capsule	81 %	98 %	250
15B	Sustained + Delayed-Release Multiparticulate	0.6 %	0.7 %	250
	43.6 % azithromycin			
	4.4 % Opadry® Solids			
	32.0 % Surelease ® Solids			
	12.3 % Eudragit® Solids			
	6.2 % Talc			
	1.5 % Triethyl Citrate			
15C	Sustained + Delayed-Release Multiparticulate	0.5 %	6.2 %	250
	42.2 % azithromycin			
	4.2 % Opadry® Solids			
	19.9 % Surelease® Solids			
	20.8 % Eudragit® Solids			
	10.4 % Talc			
	2.5 % Triethyl Citrate			

Example 16

This example illustrates a process for making sustained release azithromycin hydrophilic matrix tablets which release azithromycin at different rates depending on the extent of surface coating coverage by an aqueous insoluble polymeric barrier material as well as the composition of the hydrophilic matrix tablet core.

Tablet cores were made first by shaking (Turbula System) in a suitable size jar for about 15 minutes the following: 105 g azithromycin, 15 g. hydroxypropyl methylcellulose (HPMC, Dow Methocel® E4M-CR) and 27.75 g microcrystalline cellulose (Avicel PH-102, FMC Corp.). The resulting blend was then passed through a 40 mesh sieve and shaken for ten additional minutes. Then, 2.25 g of magnesium stearate was added and the mixture was shaken for five minutes. Using a Manesty type F press fitted with 13/32 inch standard round concave (SRC) punches, the final blend was compressed into tablet cores.

Tablet cores were made first by shaking (Turbula System) for about 15 minutes in a jar 105 g azithromycin, 15 g. hydroxypropyl methylcellulose (HPMC, Dow Methocel® E4M-CR) and 27.75 g microcrystalline cellulose (Avicel PH-102, FMC Corp.). This blend was then passed through a 40 mesh sieve and shaken for ten minutes. Then, 2.25 g of magnesium stearate was added and the mixture was shaken for five minutes. Using a Manesty type F press fitted with 13/32 inch standard round concave (SRC) punches, the final blend was compressed into tablet cores.

A delayed-release coating suspension containing 12.3 % methacrylic acid copolymers (Eudragit® L 30 D-55), 6.2 % talc, 1.5 % triethyl citrate and 80 % water was prepared and applied as a 10 % coating, using an HCT-30 Hi-Coater (Vector-Freund) to spray the solution onto the matrix tablet cores. Because the coating is soluble in environments where the pH is greater than 5.5, the tablets thus prepared release azithromycin from the hydrophilic matrix tablet cores below the stomach where the pH is greater than 5.5, and the cores do so in a sustained manner that delivers azithromycin predominantly below the duodenum.

Example 18

This example illustrates a process for making an osmotic azithromycin sustained release tablet with a bilayer (two compartment) core surrounded by a semipermeable membrane with a passage through its surface. One tablet core layer has an osmotically effective composition containing azithromycin and the second tablet core layer contains an expanding hydrogel.

The first tablet core layer material was prepared by Turbula blending for about 15 minutes 70 g polyethylene oxide having a molecular weight of 5,000,000 (Polyox® Coagulant), 23 g sodium chloride and 5 g hydroxypropyl methylcellulose (Dow Methocel® E4M) in a jar. The contents were passed through a 60 mesh sieve and collected in a jar. Then, 2 g of magnesium stearate were added and the mixture Turbula blended for 5 minutes.

The second tablet core layer material containing azithromycin was prepared by Turbula blending for about 15 minutes 50 g azithromycin, 150 g polyethylene oxide having a molecular weight of 100,000 (Polyox® N-20, Union Carbide Corp., Danbury, CT) and 10 g hydroxypropyl methylcellulose (Dow Methocel® E4M) in a jar. The contents were passed

around the tablet core which is permeable to water and impermeable to azithromycin and other tablet core excipients.

Next, different diameter passageways from .008 inch to 0.020 inch diameter were mechanically drilled through the top of the semipermeable wall connecting the exterior of the tablet with the tablet core containing the azithromycin.

Example 20

This example illustrates a process for making multiparticulates for use in making delayed-release dosage forms designed to release azithromycin predominantly below the duodenum. The process comprises (1) preparing uncoated azithromycin multiparticulate cores; (2) applying a first, sustained-release diffusion barrier coating over the cores; and (3) applying a second , pH-sensitive, delayed release coating over the first coat.

Azithromycin-containing multiparticulate cores are prepared by blending azithromycin compound with microcrystalline cellulose (Avicel® PH101, FMC Corp., Philadelphia, PA) in relative amounts of 95:5 (w/w), wet massing the blend in a Hobart mixer with water equivalent to approximately 27 % of the weight of the blend, extruding the wet mass through a perforated plate (Luwa EXKS-1 extruder, Fuji Paudal Co.,Osaka Japan), spheronizing the extrudate (Luwa QJ-230 marumerizer, Fuji Paudal Co.) and drying the final cores which are about 1 mm diameter.

Next, a Wurster bottom spray fluid bed processor (Glatt GPCG-1) is used to coat the uncoated azithromycin-containing multiparticulate with a diffusion barrier coating. A plasticized ethylcellulose (Surelease®) coating suspension diluted to 15% solids is sprayed onto the core particles. Typically, a 5 % to 20 % diffusion barrier coating is applied. The amount of barrier coating applied determines the rate of azithromycin release from the uncoated core.

Lastly, a Wurster bottom spray fluid bed processor (Glatt GPCG-1) is used to apply a delayed release coating over the diffusion barrier coated particles. Typical delayed release coating levels are 25 % to 50 % in order to be sure that the delayed release dissolution criterion are met. The delayed-release coating is a suspension containing 12.3 % methacrylic acid copolymers (Eudragit® L 30 D-55), 6.2 % talc, 1.5 % triethyl citrate and 80 % water.

applied in conventional equipment. The rate of release of drug from the coated beads is dependent on the amount of coating applied.

Drug-containing beads are prepared by blending azithromycin fumarate with microcrystalline cellulose (Avicel® CL 611. FMC) in relative amounts of 95:5, wet-massing the blend in a Hobart mixer with water until a dough is obtained, extruding the wet mass through a perforated plate (Luwa extruder), and spheronizing the extrudate (Luwa spheronizer). The beads so prepared are dried and coated in an Aeromatic Strea-1 benchtop Wurster coater (batch size 100g). The coating solution is prepared by dissolving 36g cellulose acetate (Eastman CA 398-10), 7.9g poly(ethylene glycol) (PEG 400), and the required amount of sorbitol in a mixture of methylene chloride, methanol and water (15:10:1) sufficient to bring the polymer concentration to about 2%. The coating is applied in the fluidized bed until the desired thickness is obtained. The following compositions give sustained-release of azithromycin:

Sorbitol In Coating Solution	coating thickness
3g	0.01cm
3g	0.02cm
3g	0.05cm
3g	0.10cm
6g	0.01cm
6g	0.02cm
6g	0.05cm
6g	0.10cm
12g	0.01cm
12g	0.02cm
12g	0.05cm
12g	0.10cm

Example 23

This example illustrates the preparation of tablets coated with a membrane which develops pores when placed in a use environment for sustained release of azithromycin.

Oval-shaped tablets containing 750mg azithromycin fumarate, 100mg sorbitol and 10mg magnesium stearate are prepared by compressing a

Example 26.

This example illustrates the preparation of perforated coated tablets with a copolymeric ethylene/vinyl acetate coating which deliver azithromycin from a central hole.

Tablets containing 750mg azithromycin fumarate and 100mg hydroxypropylmethylcellulose (Dow Methocel K100LV) are prepared by compressing a mixture of the powders on a Carver press using a standard round die and round flat-faced punches of 1.3cm diameter. The tablets are coated by dipping into a solution containing 10% ethylene vinyl acetate (Aldrich Chemical Co.) in methylene chloride. The coated tablets are further dried at 50°C overnight. A 2mm hole is then drilled through the center of each tablet to yield a sustained release dosage form.

Example 27.

This example illustrates preparation of perforated coated tablets which utilize a geometric approach to linearizing the release of azithromycin.

Tablets are prepared as in Example 26, except that conical punches are used to give a tablet increasing in thickness from the center outward at an angle of 30°. These tablets are completely coated by dipping into a solution of 20% cellulose acetate (Eastman CA 398-10) in acetone. The tablets are allowed to air dry, then are dried at 50° overnight. As before, a 1mm hole is drilled through the center of the tablet to yield a sustained-release dosage form

Example 28.

This example illustrates preparation of hemispherical pellets having a hole in the center of the flat face.

Azithromycin dihydrate and polyethylene (PEP-315, Union Carbide) powder are each passed through a 60 mesh screen before use. The following blends are prepared:

Example 29.

This example illustrates the preparation of coated cylindrical tablets or boluses which deliver azithromycin through slits cut in the periphery of the coating.

A blend of azithromycin is prepared with 10% HPMC and 2% magnesium stearate and compression-molded into cylinders of 1 cm and 2 cm diameter. The length of the cylinders is dependent on the amount of blend charged into the mold, as shown in the table below:

diameter	amt of blend	amt of azithromycin	length
1 cm	1 g	880 mg	1.3 cm (approx)
1 cm	2 g	1760 mg	2.6 cm
1 cm	3 g	2640 mg	3.9 cm
2 cm	3 g	2640 mg	0.84 cm
2 cm	6 g	5280 mg	1.7 cm
2 cm	12 g	10560 mg	3.4 cm

The cylinders so prepared are thoroughly coated with ethylcellulose (Dow EC S-100) by dipping into a solution of 20% EC in acetone and dried at 50°C overnight. A sharp blade is then used to cut four equidistant longitudinal slits, approximately 0.5mm wide, along the periphery of each cylinder to yield sustained-release dosage forms. These larger dosage forms are especially useful for treatment of animals, especially ruminants, which can retain the dosage forms in the rumen for a prolonged period of time.

Example 30.

This example illustrates the preparation of a delivery system consisting of a porous hydrophobic membrane capsule with an osmotic "push" compartment to drive a piston acting on any dispensable azithromycin drug composition.

A porous hydrophobic membrane capsule is prepared by the following procedure:

First glucose is milled to a 230 mesh screen size. The milled glucose (15g) is then mixed with poly(d,l-lactide) (35g, 200,000 avg. mol. wt.) and the mixture is blended and milled. A quantity (1.15g) of the resulting particles is then placed in a transfer mold where the particles are molded in the form of a membrane cup with an open end. The dimensions of the membrane cup

in a final coating polymer weight, after drying, of 20 wt%, relative to the weight of the uncoated tablet bed.

Table 31-1
Azithromycin Tablet Core Formulation

COMPONENT	WEIGHT (MG/TABLET)
Azithromycin dihydrate*	524.10
Pregelatinized starch**	54.00
Calcium phosphate dibasic, anhydrous	277.68
Sodium croscarmellose#	18.00
Magnesium stearate/Sodium lauryl sulfate (90/10)	26.22
TOTAL	900

* Based on a theoretical potency of 95.4%.
** Starch 1500
\# Ac-Di-Sol (FMC Corp.).

Example 32.

This example illustrate the preparation of a pH-Dependent CAP-Coated Tablet with Barrier Coat.

Azithromycin tablets are manufactured as described in Example 31. Tablets are spray coated with a solution of hydroxypropylmethylcellulose (HPMC; Colorcon, Inc.) in water, using a HCT-60 Hi-Coater. In this manner, tablets are coated with a 5 wt% barrier coat of HPMC, relative to the initial tablet weight. Tablets are then further spray-coated with cellulose acetate phthalate (CAP) and DEP plasticizer (as described in Example 31), in the HCT-60 Hi-Coater. Sufficient CAP is sprayed onto the tablets to result in a final coating polymer weight, after drying , of 20 wt%, relative to the weight of the uncoated tablet. The HPMC coat serves as a barrier between azithromycin and the pH-sensitive CAP coat. This barrier coat prevents premature dissolution (or weakening) of the CAP coat, e.g., in the low pH environment of the stomach, potentially caused by a locally high pH in the tablet interior due to the presence of azithromycin.

Azithromycin tablets are manufactured according to Example 31. Tablets are spray coated with a solution of hydroxypropylmethylcellulose (HPMC) (Colorcon, Inc.) in water, using a HCT-60 Hi-Coater. In this manner, tablets are coated with a 5 wt% barrier coat of HPMC, relative to the initial tablet weight. Tablets are then spray-coated with an acrylic resin in an HCT-60 Hi-Coater® spray-coating apparatus (Freund Industries Corp, Tokyo). The resin consists of a 1:1 (w/w) mixture of Eudragit-L® and Eudragit-S®, which are methacrylic acid/methyl methacrylate copolymers, provided by the RöhmPharma Corporation (Darmstadt, Germany). The formula for the spray coating solution is given in Table 33-1. The Eudragit-L/S Primary Layer coating formulation is sprayed on the tablets in the Hi-Coater, followed by spray-coating with the Covering Layer formulation. The total acrylic resin polymer weight applied is 15% of the weight of the uncoated tablet bed. The HPMC undercoat serves as a barrier between azithromycin and the pH-sensitive acrylic resin coat. This barrier coat prevents premature dissolution (or weakening) of the acrylic resin coat, e.g., in the low pH environment of the stomach, potentially caused by a locally high pH in the tablet interior due to the presence of azithromycin.

Example 35.

This example illustrates the preparation of Azithromycin Tablets with a Double Delayed Release Coat.

Azithromycin tablets are manufactured according to Example 31. Tablets are spray coated with an aqueous mixture of ethylcellulose (EC) (Surelease; Colorcon Inc.) and hydroxypropylmethylcellulose (HPMC) (Opadry®; Colorcon Inc.) at 70/30 EC/HPMC, using a HCT-60 Hi-Coater®. In this manner, tablets are coated with a 5 wt% coat of EC/HPMC, relative to the initial tablet weight. Tablets are then spray-coated with an acrylic resin in an HCT-60 Hi-Coater® spray-coating apparatus (Freund Industries Corp., Tokyo). The resin consists of a 1:1 (w/w) mixture of Eudragit-L® and Eudragit-S®, which are methacrylic acid/methyl methacrylate copolymers, available from RöhmPharma Corporation (Darmstadt, Germany). The formula for the spray coating solution is given in Table 33-1. The Eudragit-L/S Primary Layer coating formulation is sprayed on the tablets in the Hi-Coater, followed by spray-coating with the Covering Layer formulation. The total acrylic resin coating polymer weight applied is 10% of the weight of the uncoated tablet bed.

Azithromycin/microcrystalline cellulose beads were prepared as in Example 36. In a Glatt GPCG-1 Fluid Bed Processor, these beads are coated with an aqueous solution of HPMC (Opadry®, Colorcon, Inc.). The final dry HPMC barrier coat comprises 5% of the weight of the uncoated beads. The HPMC-coated azithromycin beads are then coated with a 25% (by weight) coat of acrylic resin as described in Example 36. The HPMC undercoat serves as a barrier between azithromycin and the pH-sensitive acrylic resin coat. This barrier coat prevents premature dissolution (or weakening) of the acrylic resin coat, e.g., in the low pH environment of the stomach, potentially caused by a locally high pH in the tablet interior due to the presence of azithromycin.

6. A dosage form as defined in claim 5, wherein said matrix comprises hydroxypropyl methylcellulose.

7. A dosage form as defined in claim 5, wherein said matrix comprises hydroxypropyl cellulose.

8. A dosage form as defined in claim 5, wherein said matrix comprises poly(ethylene oxide).

9. A dosage form as defined in claim 5, wherein said matrix comprises polyacrylic acid.

10. A dosage form as defined in claim 2, comprising a reservoir of azithromycin encased in a membrane which limits the release rate of azithromycin to said GI tract by diffusion.

11. A dosage form as defined in claim 10, in the form of a tablet coated with a membrane.

12. A dosage form as defined in claim 2, in the form of a multiparticulate comprising particles each of which is coated with a membrane which limits the release rate of said azithromycin by diffusion.

IMP.

13. A dosage form as defined in claim 3, wherein a portion of the outside surface of said matrix is covered with an impermeable coating and the remainder of said outside surface is uncovered.

14. A dosage form as defined in claim 13, substantially in the shape of a cylinder wherein said impermeable coating covers one or both of the opposing flat surfaces thereof.

15. A dosage form as defined in claim 13, substantially in the shape of a cylinder wherein said impermeable coating covers only the radial surface thereof.

23. A process for preparing a multiparticulate dosage form of azithromycin comprising the steps of:
a) granulating azithromycin bulk drug substance with a binder to obtain a granulation having an average particle size from about 50 to about 300 μM;
b) substantially immediately thereafter coating the granulated azithromycin with a sustained release membrane-forming material in an amount of about 5 to 30% of the total weight of the coated product; and
c) thereafter further coating the product of said step (b) with additional polymer until the total amount of polymer coating is from about 25% to about 70% of the total weight of the coated product.

24. A process as defined in claim 23, comprising the additional step of coating the product of step (c) with a pH-sensitive polymer which is soluble at a pH > 6, but insoluble at a pH < 4.

25. A process as defined in claim 24, wherein the sustained-release polymer is ethylcellulose and the pH-sensitive polymer is a copolymer of methacrylic acid and methylmethacrylate or cellulose acetate phthalate.

26. A dosage form for oral administration comprising azithromycin and a pharmaceutically acceptable carrier, which releases not more than 10% of its incorporated azithromycin into a mammal's stomach, and which releases not more than an additional 10% during the first 15 minutes after entering said mammal's duodenum.

27. A dosage form as defined in claim 26, wherein said mammal is a human.

28. A dosage form as defined in claim 26, in the form of a tablet.

29. A dosage form as defined in claim 26, comprising a multiparticulate having a diameter between about 0.5 mm and about 3 mm.

30. A dosage form as defined in claim 26, comprising a a multiparticulate having a diameter between about 0.1 and about 0.5 mm.

38. A dosage form as defined in claim 29, said multiparticulate further comprising one or more osmagents, said multiparticulate being surrounded by a semipermeable membrane that is permeable to water and substantially impermeable to azithromycin and osmagents.

39. A dosage form as defined in claim 28, further comprising at least one swellable material, said tablet being surrounded by a semipermeable membrane that is permeable to water and substantially impermeable to azithromycin and said swellable material.

40. A dosage form as defined in claim 29, further comprising at least one swellable material, each of said multiparticulate being surrounded by a semipermeable membrane that is permeable to water and substantially impermeable to azithromycin and said swellable materials.

41. A dosage form as defined in claim 28, comprising:

a core comprising azithromycin and at least one osmagent;

a wall surrounding said tablet comprising a semipermeable membrane which is permeable to water and substantially impermeable to azithromycin and osmagent; and

a pH-sensitive trigger means attached to said semipermeable membrane for triggering the bursting of the tablet, said trigger means triggering at a pH between 3 and 9.

42. A dosage form as defined in claim 29, said multiparticulate each further comprising

one or more osmagents, each multiparticulate being surrounded by a wall comprising a semipermeable membrane which is permeable to water and substantially impermeable to azithromycin and osmagent; and

a pH-sensitive trigger means attached to said semipermeable membrane for triggering the bursting of the multiparticulate said trigger means triggering at a pH between 3 and 9.

43. An azithromycin dosage form as defined in claim 41, wherein said core further comprises at least one swelling material.

a hydrophobic liquid entrained within said membrane, said hydrophobic liquid being substantially impermeable to water and azithromycin, but being capable of changing to become substantially permeable to water and azithromycin.

49. An azithromycin-containing dosage form as defined in claim 28, comprising:

a core comprising azithromycin and at least one swelling material and/or at least one osmagent;

a membrane surrounding said tablet core wherein said membrane is substantially impermeable to azithromycin and labile to enzymes produced by bacteria which inhabit the colon.

50. An azithromycin-containing dosage form as defined in claim 29, comprising:

a core comprising azithromycin and at least one swelling material and/or at least one osmagent;

a membrane surrounding said multiparticulate core wherein said membrane is substantially impermeable to azithromycin and labile to enzymes produced by bacteria which inhabit the colon.

51. An azithromycin-containing dosage form as defined in claim 49, wherein said membrane comprises a polymer comprising at least one ethylenically unsaturated monomer crosslinked by a substituted or unsubstituted divinylazobenzene.

52. An azithromycin-containing dosage form as defined in claim 50, wherein said membrane comprises a polymer comprising at least one ethylenically unsaturated monomer crosslinked by a substituted or unsubstituted divinylazobenzene.

53. An azithromycin-containing dosage form as defined in claim 49, wherein said membrane comprises at least one polysaccharide.

54. An azithromycin-containing dosage form as defined in claim 50, wherein said membrane comprises at least one polysaccharide.

60. A dosage form as defined in claim 2 in the form of a coated tablet comprising a water-soluble salt of azithromycin, said tablet having a water-permeable coating which is substantially impermeable to azithromycin and substantially non-porous, said coating containing one or more perforations or passageways, for exposing the interior of the tablet to a use environment.

61. A dosage form as defined in claim 2 in the form of a coated tablet comprising azithromycin, said tablet having a porous coating which permits transport of both water and azithromycin through said porous coating.

62. A dosage form as defined in claim 2 in the form of a coated multiparticulate formulation wherein each particle comprises azithromycin and has a porous coating which permits transport of both water and azithromycin through said porous coating.

63. A dosage form as defined in claim 1, wherein said azithromycin is embedded in a matrix, which releases said azithromycin by diffusion.

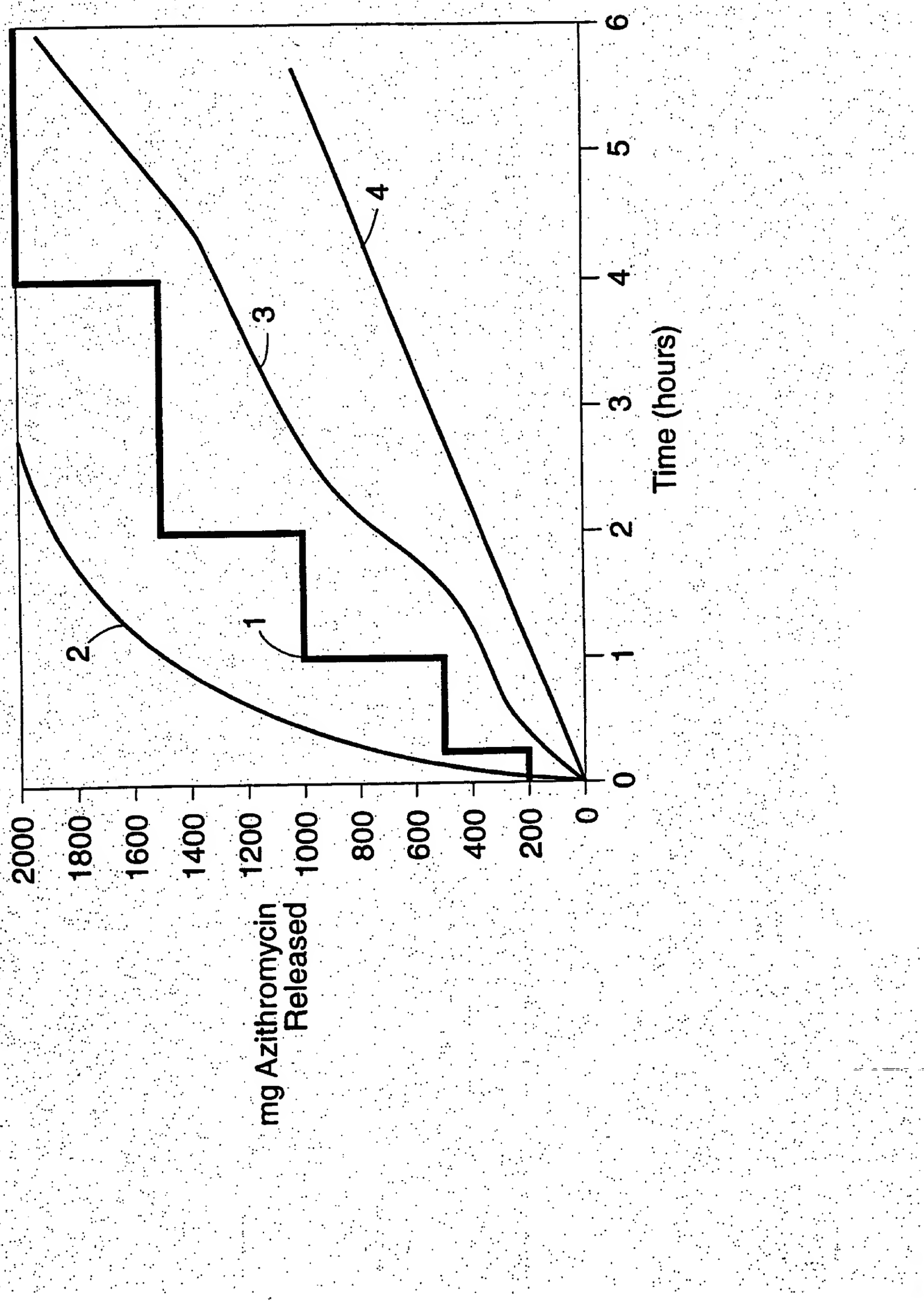
64. A dosage form as defined in claim 1, comprising a reservoir of azithromycin encased in a membrane which limits the release rate of azithromycin to said GI tract by diffusion.

65. A dosage form as defined in claim 1, in the form of a multiparticulate comprising particles each of which is coated with a membrane which limits the release rate of said azithromycin by diffusion.

66. A method of treating a mammal with azithromycin with a reduced incidence of gastrointestinal side effects relative to a bolus oral dose, said method comprising dosing an azithromycin-containing dosage form as defined in claim 1.

67. A method of treating a mammal with azithromycin with a reduced incidence of gastrointestinal side effects relative to a bolus oral dose, said method comprising dosing an azithromycin-containing dosage form as defined in claim 26.

FIG. 1


mg Azithromycin Released
2000
1800
1600
1400
1200
1000
800
600
400
200
0
0
1
2
3
4
5
6
Time (hours)
1
2
3
4

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
E	WO,A,95 09601 (THE PROCTER & GAMBLE COMPANY,U.S.A.) 13 April 1995 see claims 1-3,6-9 see page 4, line 20 - line 27 see page 4, line 36 - line 38 see page 5, line 8 - line 15 see page 5, line 29 - line 39	1,6,7,9, 11,26-28

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Remark: Although claims 22,56,66-67 are directed to a method of treatment of the human body by therapy (Rule 39.1(iv)PCT) the search has been carried out and based on the alleged effects of the composition.

2. [ ] Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. [ ] As all searchable claims could be searches without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.